

Claims 5 and 6 stand rejected under the judicially created doctrine of obviousness type doubling patenting as being unpatentable over claims 1 and 2 over U.S. Patent No. 6,046,319. Accordingly, a terminal disclaimer is enclosed herewith thus overcoming the present rejection.

Claims 5, 9, and 11-12 stand rejected under 35 U.S.C. § 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Office Action states that claims 5 and 9 provide for the use of an antisense oligonucleotide and a pharmaceutical composition, respectively, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intending to encompass. Accordingly, claims 5 and 9 have been amended to more specifically recite what is being claimed. Namely, that the claims are not method claims but instead are pharmaceutical claims and therefore do not require steps. Reconsideration of the rejection is respectfully requested.

The Office Action states that claims 5 and 11-12 recite "targeting exon sequences flanking donors splice sites thereby regulating expression of TNF- $\alpha$ ", the Office Action states that this phrase is vague and indefinite. However, there is

sufficient disclosure in the specification at pages 2, lines 8-18 and page 8, line 24-page 9, line 5 which sufficiently disclosed what is meant by this phrase. Accordingly, reconsideration of the rejection is respectfully requested.

Claims 3-4, 7-9, 10 and 13-16 stand rejected under 35 U.S.C. § 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office Action states that while the specification is enabling for inhibiting the expression of TNF- $\alpha$  *in vitro*, it does not reasonably provide enablement for modulating, which includes for enhancing and inhibiting, the expression of TNF- $\alpha$ , *in vivo*. In order to further prosecution, the claims have been amended to specifically recite only inhibiting the expression of TNF- $\alpha$ . Thus overcoming a portion of the present rejection.)

The Office Action also states that the specification as filed does not disclose a successful *in vivo* delivery of the antisense/ribozyme compounds and that such knowledge is not currently known in the art. The Office Action states that the current state of the art teaches that the behavior of antisense oligonucleotides *in vivo* and *in vitro* is unpredictable. However, as set forth in the attached paper by Applicants, there is disclosed that the *in vivo* use of the method as set forth in the

present application does perform as indicated in the *in vitro* studies. Specifically, the attached article shows data collected by the Applicants utilizing the methods of the present invention in rats. This study shows that rats treated with the methods and compositions of the present application developed the results which were predicted based upon the *in vitro* study. Accordingly, there is sufficient support for the specification as currently pending, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES



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**CERTIFICATE OF TRANSMISSION BY MAIL**

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on August 8, 2000.



Marie M. DeWitt